enhanced cytotoxicity in various cancer cells. In this study, we evaluated the effect of combination therapy with DNA-damaging drugs and a macrolide antibiotic.

We found that DNA-damaging drugs in combination with azithromycin (AZM), one of the macrolide antibiotics, enhanced cell death including apoptosis in a non-small cell lung cancer cell line, A549. This enhanced cytotoxicity by the drug combinations was significantly decreased in a p53-mutated lung cancer cell line and a p53 KO A549 cells. We also found that the combined use of a DNA-damaging drug and AZM significantly changed the morphology with an increased number of the enlarged LAMP2-positive organelles which were considered as autolysosomes and/or lysosomes. These data suggested that DNA-damaging drugs in combination with AZM strongly induced cell death in A549 cells by activating apoptosis which might be caused by the damaged lysosomes and dependent on the p53 signaling pathway.

3-I-2.

Increased APOBEC3C-H Gene Expression is Associated with Improved Outcome in Breast Cancer

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Background : APOBEC3 are strong mutagenic enzymes. The association between APOBEC3B (A3B) expression and DNA mutation has been well studied. However, it is still unclear on other A3s (A3A, C-H). We investigated the clinical relevance of A3s on their mutagenic and cancer immunity angles.
Methods : 1) A3s gene expression level was examined on 55 breast cancer cell lines.

2) The association of A3s with the clinical outcome and other molecular features were investigated from TCGA-BRCA data. Patients were divided into 3 groups by the A3s gene expression level ; high, intermediate and low. The clinical outcome were compared between high and low groups. Molecular features were quantified with bioinformatics workflow and examined the association with A3s expression level.
Results : 1) A3B & 3C represented 91% of A3s expression in cell lines. 2) A3C-H expression was significantly associated with improved clinical outcome (HR, 0.45-0.66). A3A and A3B expression levels were correlated with both tumor mutation burden and neoantigen load (Spearman r = 0.28-0.34), while not for A3C-H. Expression of genes related to immune function like interferon response and complement activation was enriched in high A3C-H expressors, which significance was observed in CD4 and CD8 T cells, TCR diversity and tumor immune cytolytic activity (2.3-4.0x, 2.1-5.4x, 1.3-2.1x & 3.1-7.9x, resp.).
Conclusion : Unlike A3B, A3C-H were expressed in stromal cells, not in breast cancer cells. A3C-H expression may activate immune cells. A3C-H gene expression was associated with better outcome in breast cancer patients. It is speculated that up-regulating immune function by A3C-H may explain this clinical finding.